We Claim:

1. A process of making a genetically engineered neisserial strain with a LOS immunotype of reduced phase variability comprising the steps of:
a) selecting a neisserial strain with phase-variable LOS synthesis, and
b) genetically engineering said strain such that the homopolymeric nucleotide tract of a phase-variable LOS oligosaccharide synthesis gene is modified to render the expression of said gene less phase variable.

2. The process of claim 1, wherein the LOS oligosaccharide synthesis gene is modified to render the expression of said gene non-phase variable.

3. The process of claim 1 or 2, to make a genetically engineered neisserial strain with a LOS immunotype which is non-phase variable.

4. The process of claims 1-3, wherein the neisserial strain is a meningococcal strain, preferably meningococcus B.

5. The process of claims 1-4, to make a genetically engineered neisserial strain with an L2 LOS immunotype.

6. The process of claim 5, wherein in step a) a neisserial strain with phase-variable L2 LOS synthesis is selected.

7. The process of claim 5 or 6, wherein step b) comprises the step of fixing the expression of the lgtA gene product.

8. The process of claim 7, wherein the expression of the lgtA gene product is fixed by reducing the length of the homopolymeric nucleotide tract within the open-reading frame of the gene whilst maintaining the open-reading frame in frame.

9. The process of claim 8, wherein the homopolymeric G tract in the lgtA open-reading frame is reduced to 8, 5 or 2 consecutive G nucleotides.

10. The process of claims 7-9, wherein the expression of lgtA gene product is fixed by changing the sequence of the homopolymeric G nucleotide tract within the open-reading frame of the lgtA gene such that: one or more GGG codons encoding Glycine is changed to any other codon encoding glycine, or a codon encoding a conservative mutation, and/or the TCG codon encoding Serine is changed to any other codon encoding Serine, or a codon encoding a conservative mutation, whilst maintaining the open-reading frame of the gene in frame.

11. The process of claim 10, wherein 2, 3 or 4 codons in the homopolymeric tract are changed, preferably to encode the identical amino acid.

12. The process of claims 5-11, wherein step b) comprises the step of fixing the expression of the lgtG gene product.

13. The process of claim 12, wherein the expression of the lgtG gene product is fixed by reducing the length of the homopolymeric nucleotide tract within the open-reading frame of the gene whilst maintaining the open-reading frame in frame.

14. The process of claim 13, wherein the homopolymeric C tract in the lgtG open-reading frame is reduced to 8, 5 or 2 consecutive C nucleotides.

15. The process of claims 12-14, wherein the expression of lgtG gene product is fixed by changing the sequence of the homopolymeric C nucleotide tract within the open-reading frame of the lgtG gene such that: one or more CCC codons encoding Proline is changed to any other codon encoding Proline, or a codon encoding a conservative mutation, and/or the GCC codon encoding Alanine is changed to any other codon encoding Alanine, or a codon encoding a conservative mutation, whilst maintaining the open-reading frame of the gene in frame.

16. The process of claim 15, wherein 2, 3 or 4 codons in the homopolymeric tract are changed, preferably to encode the identical amino acid.

17. The process of claim 5 or 6, wherein step b) comprises the steps of fixing the expression of the lgtA gene product by reducing the length of the homopolymeric G nucleotide tract within the open-reading frame of the gene to 5 or 2 consecutive G nucleotides whilst maintaining the open-reading frame of the gene in frame (and optionally changing the sequence of the homopolymeric G nucleotide tract such that: one or more GGG codons encoding Glycine is changed to any other codon encoding glycine, or a codon encoding a conservative mutation, and/or the TCG codon encoding Serine is changed to any other codon encoding Serine, or a codon encoding a conservative mutation, whilst maintaining the open-reading frame of the gene in frame), and fixing the expression of the lgtG gene product by changing the sequence of the homopolymeric C nucleotide tract within the open-reading frame of the lgtG gene such that: 1, 2 or 3 CCC codons encoding Proline is changed to any other codon encoding Proline, or a codon encoding a conservative mutation, and/or the GCC codon encoding Alanine is changed to any other codon encoding Alanine, or a codon encoding a conservative mutation, whilst maintaining the open-reading frame of the gene in frame.

18. The process of claims 1-4, to make a genetically engineered neisserial strain with an L3 LOS immunotype.

19. The process of claim 18, wherein in step a) a neisserial strain with phase-variable L3 LOS synthesis is selected.

20. The process of claim 18 or 19, wherein step b) comprises the step of fixing the expression of the lgtA gene product.

21. The process of claim 20, wherein the expression of the lgtA gene product is fixed by reducing the length of the homopolymeric nucleotide tract within the open-reading frame of the gene whilst maintaining the open-reading frame in frame.

22. The process of claim 21, wherein the homopolymeric G tract in the lgtA open-reading frame is reduced to 8, 5 or 2 consecutive G nucleotides.

23. The process of claims 20-22, wherein the expression of lgtA gene product is fixed by changing the sequence of the homopolymeric G nucleotide tract within the open-reading frame of the lgtA gene such that: one or more GGG codons encoding Glycine is changed to any other codon encoding glycine, or a codon encoding a conservative mutation, and/or the TCG codon encoding Serine is changed to any other codon encoding Serine, or a codon encoding a conservative mutation, whilst maintaining the open-reading frame of the gene in frame.

24. The process of claim 23, wherein 2, 3 or 4 codons in the homopolymeric tract are changed, preferably to encode the identical amino acid.

25. The process of claims 18-24, wherein step b) comprises the step of permanently downregulating the expression of functional gene product from the lgtG gene.

26. The process of claim 25, wherein the expression of functional gene product from the lgtG gene is switched off, preferably by deleting all or part of the promoter or open-reading frame of the gene.

27. The process of claim 18 or 19, wherein step b) comprises the steps of fixing the expression of the lgtA gene product by reducing the length of the homopolymeric G nucleotide tract within the open-reading frame of the gene to 2 consecutive G nucleotides whilst maintaining the open-reading frame of the gene in frame, and switching off the expression of functional gene product from the lgtG gene by deleting all or part of the promoter or open-reading frame of the gene.

28. The process of claims 5-27, wherein step b) comprises the step of permanently downregulating the expression of functional gene product from the lgtC gene,

preferably by switching the gene off, most preferably by deleting all or part of the promoter or open-reading frame of the gene.

29. The process of claims 5-28, wherein step a) comprises the step of selecting a neisserial strain that is lgtB$^-$, or step b) additionally comprises the step of genetically engineering said strain such that the expression of functional gene product from the lgtB or lgtE gene is permanently downregulated, preferably by switching the gene off, most preferably by deleting all or part of the promoter or open-reading frame of the gene.

30. The process of claims 5-29, wherein step a) comprises the step of selecting a neisserial strain that is unable to sythesise capsular polysaccharide, or step b) additionally comprises the step of genetically engineering said strain such that it is unable to sythesise capsular polysaccharide, preferably by permanently downregulating the expression of functional gene product from one of the following genes: siaD (also known as synD), ctrA, ctrB, ctrC, ctrD, synA (equivalent to synX and siaA), synB (equivalent to siaB) or synC (equivalent to siaC), more preferably by switching the gene off, most preferably by deleting all or part of the promoter or open-reading frame of the gene.

31. The process of claims 5-30, wherein step a) comprises the step of selecting a neisserial strain that is msbB$^-$ and/or htrB$^-$, or step b) additionally comprises the step of genetically engineering said strain such that the expression of functional gene product from the msbB and/or htrB gene(s) is permanently downregulated, preferably by switching the gene(s) off, most preferably by deleting all or part of the promoter or open-reading frame of the gene(s).

32. A process of isolating L2 LOS comprising the steps of producing a genetically engineered neisserial strain with a fixed L2 immunotype by the process of claims 5-17, and 28-31; and isolating L2 LOS from the resulting strain.

33. The process of claim 32, comprising the additional step of conjugating the L2 LOS to a carrier comprising a source of T-cell epitopes and/or the step of presenting the L2 LOS in a liposome formulation.

34. A process of isolating neisserial blebs having an L2 LOS immunotype, comprising the steps of producing a genetically engineered neisserial strain with a fixed L2 immunotype by the process of claims 5-17, and 28-31; and isolating blebs from the resulting strain.

35. The process of claim 34, where the step of isolating blebs involves extraction with 0-0.3%, preferably 0.05-0.2%, most preferably around or exactly 0.1% deoxycholate.

36. The process of claim 34 or 35, comprising the additional step of intra-bleb conjugating the L2 LOS to an outer membrane protein also present in the blebs.

37. A process of isolating L3 LOS comprising the steps of producing a genetically engineered neisserial strain with a fixed L3 immunotype by the process of claims 18-31; and isolating L3 LOS from the resulting strain.

38. The process of claim 37, comprising the additional step of conjugating the L3 LOS to a carrier comprising a source of T-cell epitopes and/or the step of presenting the L3 LOS in a liposome formulation.

39. A process of isolating neisserial blebs having an L3 LOS immunotype, comprising the steps of producing a genetically engineered neisserial strain with a fixed L3 immunotype by the process of claims 18-31; and isolating blebs from the resulting strain.

40. The process of claim 39, where the step of isolating blebs involves extraction with 0-0.3%, preferably 0.05-0.2%, most preferably around or exactly 0.1% deoxycholate.

41. The process of claim 39 or 40, comprising the additional step of intra-bleb conjugating the L3 LOS to an outer membrane protein also present in the blebs.

42. A process of making an immunogenic composition comprising the steps of producing isolated L2 LOS by the process of claims 32-33 or producing isolated neisserial blebs having an L2 LOS immunotype by the process of claims 34-36, and formulating said L2 LOS or blebs with a pharmaceutically acceptable excipient.

43. A process of making an immunogenic composition comprising the steps of producing isolated L3 LOS by the process of claims 37-38 or producing isolated neisserial blebs having an L3 LOS immunotype by the process of claims 39-41, and formulating said L3 LOS or blebs with a pharmaceutically acceptable excipient.

44. A process of making a multivalent immunogenic composition comprising the steps of producing isolated L2 LOS by the process of claims 32-33 or producing isolated neisserial blebs having an L2 LOS immunotype by the process of claims 34-36, producing isolated L3 LOS by the process of claims 37-38 or producing isolated neisserial blebs having an L3 LOS immunotype by the process of claims 39-41, and mixing said L2 and L3 components together along with a pharmaceutically acceptable excipient.

45. A process of growing a high cell density of an L2 or L3 neisserial strain comprising the steps of:

a) genetically-engineering a neisserial strain according to claims 5-31;

b) growing the strain to high cell density in a fermentor.

46. The process of claim 45, wherein the strain is grown to a cell density of OD_{450} 10-19, preferably 12-16, in iron non-limiting conditions, or 6-12, preferably 8-10, in iron limited conditions.

47. A process of isolating neisserial L2 or L3 LOS comprising the steps of growing an L2 or L3 neisserial strain to high cell density according to the process of claim 45 or 46, and isolating L2 or L3 LOS from the resulting strain.

48. The process of claim 47, comprising the additional step of conjugating the L2 or L3 LOS to a carrier comprising a source of T-cell epitopes and/or the step of presenting the L2 or L3 LOS in a liposome formulation.

49. A process of isolating neisserial blebs having an L2 or L3 LOS immunotype, comprising the steps of growing an L2 or L3 neisserial strain to high cell density according to the process of claim 45 or 46; and isolating blebs from the resulting strain.

50. The process of claim 49, where the step of isolating blebs involves extraction with 0-0.3%, preferably 0.05-0.2%, most preferably around or exactly 0.1% deoxycholate.

51. The process of claim 49 or 50, comprising the additional step of intra-bleb conjugating the L2 or L3 LOS to an outer membrane protein also present in the blebs.

52. A process of making an immunogenic composition comprising the steps of producing isolated L2 or L3 LOS by the process of claims 47-48 or producing isolated neisserial blebs having an L2 or L3 LOS immunotype by the process of claims 49-51, and formulating said L2 or L3 LOS or blebs with a pharmaceutically acceptable excipient.

53. A process of making a multivalent immunogenic composition comprising the steps of producing isolated L2 LOS by the process of claims 47-48 or producing isolated neisserial blebs having an L2 LOS immunotype by the process of claims 49-51, producing isolated L3 LOS by the process of claims 47-48 or producing isolated neisserial blebs having an L3 LOS immunotype by the process of claims 49-51, and

mixing said L2 and L3 components together along with a pharmaceutically acceptable excipient.